85 Pharmacokinetics of continuous treatment with o.d. or b.i.d. inhalation of tobramycin (TOBI™)

E. Rietschel[1], D. Staab[2], S. von Konigsbruggen[1], N. Merkel[3], H.-E. Heuer[4], H.-G. Posselt[5]. [1]*CF Center, University Children's Hospital, Cologne, Germany;* [2]*CF Center, Children's Hospital Charité, Berlin, Germany;* [3]*University Children's Hospital, Halle, Germany;* [4]*CF Center, Hamburg-Altuna, Germany;* [5]*University Children's Hospital, Frankfurt, Germany*

Introduction: Twice daily (b.i.d.) inhalation of TOBI™ (300 mg/5 mL) in a 28-day on/off-dosing regimen has previously proven its safety and efficacy for the treatment of *Pseudomonas aeruginosa* (P.a.) in CF subjects.
This randomized, open label, cross-over study explored the impact of of continuous o.d. (1×300 mg/d) and b.i.d. (2×300 mg/d) treatment of TOBI™ via PARI eFlow™ rapid on pharmacokinetics (PK) after 4 and 8 wks in CF patients chronically infected with P.a. The primary endpoint was serum PK of tobramycin ($AUC_{0-90'}$). Further objectives were safety, change in MIC of P.a. and lung function.
Results: 24 of 29 randomized patients completed both treatment regimens, mean age was 19.8 (range: 8–35) yrs. For o.d. treatment, serum levels were 20% higher after 8 wks compared with 4 wks ($AUC_{0-90'}$ ratio: 1.203, 95% CI: 0.818–1.468) whereas under b.i.d. treatment there was a 40% decrease after 8 wks compared to 4 wks ($AUC_{0-90'}$ ratio: 0.608, 95% CI: 0.435–10.850). $AUC_{0-90'}$ of o.d. and b.i.d. after 8 wks did not differ significantly.
Overall number of patients reporting an AE was similar among treatment groups: o.d. N = 20 (76.9%) and b.i.d. N = 21 (75.0%). Most common AEs were nasopharyngitis, headache and cough. Three SAEs have been reported (exacerbation, orthostatic dysregulation and aspergillosis), none was considered related to treatment.
Conclusion: Results from this study indicate acceptable safety and tolerability of continuous treatment with TOBI™ and justify exposure of larger populations to alternative treatment regimens in future studies.

86* Effects of inhaled MP-376 (aeroquin, levofloxacin inhalation solution) on lung function in stable cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* (PA) lung infection

P. Flume[1], D.E. Geller[2], L. Sindel[3], D. Staab[4], R. Fischer[5], J. Riethmüller[6], J. Loutit[7], D. Conrad[8], Mpex 204 Study Group. [1]*Medical University of South Carolina, Charleston, SC, United States;* [2]*Nemours Children's Clinic, Orlando, FL, United States;* [3]*Pulmonary Associates of Mobile, Mobile, AL, United States;* [4]*Charité-University Hospital Berlin, Berlin, Germany;* [5]*Med. Klinik Innenstadt, Munich, Germany;* [6]*Universitäts-Kinderklinik Tübingen, Baden-Württemberg, Germany;* [7]*Mpex Pharmaceuticals, San Diego, CA, United States;* [8]*University California San Diego, San Diego, CA, United States*

Introduction: New inhaled antimicrobials for CF patients are needed due to increased resistance, decreased efficacy and poor compliance/tolerability. This study assessed the efficacy and safety of MP-376, a novel levofloxacin formulation for inhalation, in CF patients with extensive previous use of inhaled antibiotics.
Methods: Randomized, double-blind, placebo controlled trial of 3 dose groups of MP-376 (120 mg QD, 240 mg QD, 240 mg BID) vs. placebo for 28 days, delivered by a customized investigational PARI eFlow nebulizer. Inclusion criteria: age ⩾16 years, chronic PA airways infection, FEV1 between 25–85% predicted, and ⩾3 courses of inhaled antibiotics over the past 12 months.
Results: 151 patients enrolled with mean baseline characteristics of age 29 years, FEV1 52% of predicted, and 4.8 courses of inhaled antibiotics over last 12 months. Concomitant respiratory medications included dornase-alpha (78%), azithromycin (74%), and hypertonic saline (46%). Improvement in lung function was observed in all dose groups, the largest seen with 240 mg BID. At Day 28, improvements over placebo in this group were change in FEV1 8.6% ($p = 0.0026$), relative change in percent predicted FEV1 10.9% ($p = 0.0008$), change in FVC 5.7% ($p = 0.0221$) and change in FEF 25–75 22.3% ($p < 0.0001$). Statistically significant results were also observed in all MP-376 dose groups for sputum PA density reduction and in time to need for inhaled and/or systemic anti-PA antimicrobials.
Conclusion: Nebulized MP-376 (Aeroquin) demonstrated statistically and clinically significant improvement in lung function in this heavily-treated CF patient population with PA lung infection. Phase 3 studies are planned.

87 Pharmacokinetics (PK) of aerosol MP-376 (aeroquin; levofloxacin inhalation solution) in CF patients

D.E. Geller[1], P.A. Flume[2], D.C. Griffith[3], E. Morgan[3], D. White[3], J. Loutit[3], M.N. Dudley[3]. [1]*Nemours Children's Clinic, Orlando, FL, United States;* [2]*Medical University of South Carolina, Charleston, SC, United States;* [3]*Mpex Pharmaceuticals, San Diego, CA, United States*

Objective: MP-376 is a novel inhaled formulation of levofloxacin. We compared the safety, tolerability, and PK profile of MP-376 (50 and 100 mg/mL) at 2 dose levels in stable CF patients.
Methods: We enrolled 10 CF patients ⩾16 yrs old who received in random order and separated by a 7-day washout period a single 180 mg dose of each formulation. After an additional 7-day wash-out, patients received 7 consecutive days of 240 mg QD (100 mg/ml). MP-376 was delivered with an investigational eFlow nebulizer. Serum and sputum levofloxacin levels were obtained at intervals over 24 hours after each 180 mg dose and after the last 240 mg dose.
Results: The mean sputum levofloxacin PK values with the 180 mg dose delivered as 50 vs 100 mg/ml were: Cmax 2,563 vs. 2,932 mg/L; AUC 1,891 vs 1,961 mg·h/L respectively. Corresponding serum Cmax values were: 0.95 vs 1.28 mg/L and AUC 8.1 vs 9.8 mg·h/L (not statistically significant). After 7-days of 240 mg QD dosing, the sputum Cmax was 4,691 mg/L and AUC was 4,571 mg·h/L. The serum Cmax and AUC increased proportionally with dose. Delivery time was shorter with the higher concentration, and was 4–6 minutes for the 240 mg dose. MP-376 was safe and well tolerated at both doses and concentrations.
Conclusions: MP-376 provides high sputum levofloxacin concentrations resulting in high PK-PD indices for CF pathogens, and low serum exposures. MP-376 (100 mg/ml) enables delivery of 240 mg doses in 4–6 minutes and is being advanced into Phase 3 clinical trials.

88* Sinonasal inhalation of dornase alfa reduces rhinosinusitis symptoms in CF. Results of a DBPC-cross-over study

J.G. Mainz[1], I. Schiller[1], A. Koitschev[2], C. Koitschev[2], J. Riethmüller[3], B. Wiedemann[4], J.F. Beck[1]. [1]*University of Jena, CF-Centre/Paediatric Pulmonology, Jena, Germany;* [2]*Stuttgart Medical Centre, Otorhinolaryngology, Stuttgart, Germany;* [3]*University of Tübingen, Paediatrics, Tuebingen, Germany;* [4]*University of Dresden, Biometrics, Dresden, Germany*

Introduction: The upper airways are regularly affected in CF and rhinosinusitis relevantly impairs patients' quality of life and overall health. In general the sinonasal compartment is not reached by conventional inhalatory therapy but the new Pari Sinus device was shown to deliver aerosol into paranasal spaces by scintigrafic studies in humans. Previously, we presented preliminary data from 5 CF-patients included in our DBPC pilot-study on sinonasal inhalation of dornase alfa with the device.
Methods: Now we present the results from the consecutive principal study including 23 CF patients (11f, mean age 21.7 yrs) randomised to inhale either dornase alfa or 0.9% NaCl for 28 days and, after a wash-out period of 28 days, crossed over to the alternative treatment. Primary outcome parameters assessed was the Sino-Nasal-Outcome-Test (SNOT-20) a disease-specific quality of life tool.
Results: Whereas normal saline was not associated with relevant changes in SNOT-20 scores, dornase alfa improved quality of life ($p = 0.005$). Primary nasal parameters "obstruction", "sneezing or running nose", "mucopurulent secretions", "reduced sense of smelling", and "facial pain" improved with verum ($p = 0.003$) but not with isotonic saline. Also FEV1 increased significantly with verum ($p = 0.024$). Sinonasal inhalation regularly was well tolerated except in two patients who suffered from self-limiting epistaxis.
Conclusion: Even in the short period of 4 weeks of treatment the new method of sinonasal inhalation of dornase alfa led to significant reduction of sinonasal symptoms in CF-patients.